PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Distribution and specificity of high-sensitivity cardiac troponin T in older adults without acute cardiac conditions: cross-sectional results from the population-based AugUR study
AUTHORS	Dietl, Alexander; Zimmermann, Martina; Brandl, Caroline; Wallner, Stefan; Burkhardt, Ralph; Maier, Lars; Luchner, Andreas; Heid, Iris; Stark, Klaus

VERSION 1 – REVIEW

REVIEWER	Lindahl, Bertil Uppsala Clinical Research Center
REVIEW RETURNED	14-May-2021

GENERAL COMMENTS	The aim of the present study was to provide a hsTnT reference-distribution and to assess the 5 specificity of the 14ng/l cut-off value in the mobile population ≥70years of age. The authors conclude that in the elderly population without acute myocardial infarction, hsTnT increases with age and shows different levels for men and women. The specificity of the 14ng/l cut-off is considerably lower than 99%, even in healthy elderly subjects. The study is well-performed and reported and is of interested to clinicians dealing with patients with suspicion of myocardial infarction/injury. I have only have a few questions, comments and suggestions. 1. The authors are to be congratulated reporting the 95 % CI of the 99th percentiles, which unfortunately is often not done in many studies. The large confidence intervals illustrate one of the problems of using the 99th percentile, e.g. in men 70-79 yrs the 99th percentile level (70 ng/L) showed a very large CI 42 – 281 despite that the number of men between 70-79 years were quite large, 433 (table 5). Please, discuss the wide CI in the discussion/limitation section. 2. The 4th Universal definition of MI recommends sex divided 99th percentile levels, which seldom is done for cTnT (in contrast to cTnI). This study provides strong arguments for that this should also be done for cTnT. Please add some comments on that in the discussion section. 3. Please also compare the results on cTnT and age/sex with the corresponding literature on cTnI. 4. As the author point out the increasing levels of cTnT by age have several causes. One is the increase by age itself (as illustrated that also “super healthy” elderly have higher levels) and another is the increase of comorbidities associated with chronic myocardial injury by age. Please expand a little on this in the clinical implication section.

	5. Please in the limitation section, mention the limited (understandably) number of very elderly in the cohort (see comment 1) and how this affect the interpretation.

REVIEWER	McEvoy, John John Hopkins University School of Medicine, Medicine, Cardiology
REVIEW RETURNED	25-Jun-2021

GENERAL COMMENTS	This is a nice study of adults over 70, one with some clinical relevance and that was rigorously conducted inclusive of imaging for subclinical heart disease etc. Of course, one size should not fit all when it comes to any diagnostic biomarker; and high sensitivity troponin is no different in this regard. So, the motive for the study is sound. However, guidelines tend to want to reduce their recommendations to as basic and memorable a form as possible (thus the attraction to often provide generic cutpoints for clinical tests), even though it is well known that things like gender and age and other comorbidities often affect the distribution of clinical test results. In the case of troponin, there is a further motivation to provide a one size fits all cutpoint, because in so doing one generally doesn't suffer in terms of sensitivity (indeed in the case of hs-troponin-T, which increases with age, the 14ng/L cutpoint is derived from a young group and so the sensitivity of this cutpoint is not harmed by applying it to older age groups). That's not to say there is no argument for making different (more personalized) cutpoints based on things like age and gender. Indeed, but applying the 14 ng/L threshold universally, the current authors show that we lose specificity in older persons. However, I would stress that for troponin, it is sensitivity that matters most. Unfortunately, the authors do not report sensitivities, because they cannot. Another downside to this paper is that the hsTnT information on age is not new. See reports like https://www.jacc.org/doi/full/10.1016/j.jacc.2013.12.032 that have already demonstrated this (though the authors include more extreme ages, which is of some incremental value). My personal feeling is that this paper would be a better fit at a clinical chemistry journal. The authors do not report on response rates among those invited to participate in AugUR, specifically in terms of how many of those invited actually attended the study. This has implications for generalizability and should be reported. In terms of the health subgroup analyses, I agree with the author's exclusions; however, I think they should consider also excluding persons with significantly elevated BP at the study exam (say BPs >140/90 and certainly >160/100 mmHg) from subcohorts 2 and 3. See these papers. https://pubmed.ncbi.nlm.nih.gov/25880403/ https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.114.014364. The authors don't need to exclude persons with HTN or on BP meds, to do so would be implausible for such an old sample, however, excluding very elevated blood pressures at the time of biomarker testing is probably warranted for the health subgroup analyses. Although they can by intuited from the legend/title, the statistical methods used in figure 3 are not described in the statistics section and should be. Minor comment. Page 2, line 5, would 'ambulatory' be better than 'mobile'? Also, same goes for page 2 lines 9 and 13, indeed throughout the entire paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

We thank the reviewer for the time and effort to review our manuscript and for the valuable remarks. We have revised the manuscript accordingly and itemize our response to each comment below.

1. The authors are to be congratulated reporting the 95 % CI of the 99th percentiles, which unfortunately is often not done in many studies. The large confidence intervals illustrate one of the problems of using the 99th percentile, e.g. in men 70-79 yrs the 99th percentile level (70 ng/L) showed a very large CI 42 – 281 despite that the number of men between 70-79 years were quite large, 433 (table 5). Please, discuss the wide CI in the discussion/limitation section.

We thank the reviewer for appreciating our effort on precise reporting of data. Indeed, the large confidence intervals mirror one of the problems in pinpointing extreme percentiles. The reviewer mentions exemplarily the confidence interval in men aged 70 to 79 years, whose 99th percentile is 70ng/l with a large 95% CI (42 – 281). Leave-one-out analyses revealed an influential observation spreading the confidence intervals in this specific group: one man (age 77years, eGFR 59ml/min/1.73, no coronary artery disease, LVMi 117g/m2, EF 65%) exhibited an extraordinarily elevated hsTnT-level of 421ng/l. Excluding it, the 95% confidence interval decreased substantially to 38 – 101. This person was also part of two other subgroups (men and eGFR<60 ml/min/1.73m^2). Leave one out analysis resulted in slightly changed 99th percentiles and narrowed 95% confidence intervals for men (57 ng/l [46 - 75] instead of 64 [46 - 102]) and for subjects with eGFR<60 ml/min/1.73m^2 (74 [55 - 93] compared to 77 [56 - 308]).
We thank the reviewer for his attention to this aspect, which helped to clarify the wider CIs.
We show still the original values in Table 5, but report now on the leave-one-out analysis in the figure legend (Table 5, p. 15-16):

"*Leave-one-out analyses revealed an influential observation: one man (age 77years, eGFR 59ml/min/1.73, no coronary artery disease, LVMi 117g/m2, EF 65%) exhibited an extraordinarily elevated hsTnT-level of 421ng/l. Excluding it, percentiles and 95% confidence intervals were lowered to †57 [46 - 75], ‡63 [38 - 101] and §74 [55 - 93] for the 99th percentiles in ng/l [95%CI] and ‖ 31 [30 - 33], ¶ 29 [26 – 33] and Δ43 [33 – 49] for the 95th percentiles in ng/l [95%CI]."

2. The 4th Universal definition of MI recommends sex divided 99th percentile levels, which seldom is done for cTnT (in contrast to cTnI). This study provides strong arguments for that this should also be done for cTnT. Please add some comments on that in the discussion section.

We thank the reviewer for this valuable remark, which strengthened our discussion by contributing to a clinically important, on-going debate. The discussion section was amended by the following paragraph (Discussion, p. 23, lines 7 et seq.):

"Discussion
(…) Previous studies[1–3] showed lower levels of high sensitivity troponins among women compared to men. As we report on hsTnT-distribution in an age group frequently seen in chest pain units and emergency departments[4], our results may provide an argument for sex specific thresholds. Indeed,

the fourth universal definition of myocardial infarction[5] recommends the sex specific 99th percentile as upper reference limits for high sensitivity troponin assays. However, there is an on-going debate, whether sex-specific reference limits may improve prognosis in patients[6–8]. Our study encourages further analysis of hsTnT-levels in the population as well as in the emergency departments to advance clinical decision making with an improved accounting for sex differences and old age. However, As age- or sex-specific higher rule-out cut-off values barely improved the diagnostic performance of the ESC algorithm, but increased diagnostic complexity[9], . Therefore, the 2020 ESC guidelines continue to recommend uniform cut-off concentrations. At the same time, the importance of an integrative decision pathway based on full clinical assessment, electrocardiogram, hsTroponin-levels and non-invasive imaging was stressed [10]. To advance interpretation of the jigsaw piece "hsTnT" in clinical decision making, our study contributes by providing specificity data of the uniform rule-out cut-off value of 14ng/l as well as age-specific 99th percentiles of hsTnT for different strata (old versus very old age, sex, regular renal function, lack of cardiac disease history, regular left ventricular shape and function) in the mobile elderly population aged 70 years or older."

3. Please also compare the results on cTnT and age/sex with the corresponding literature on cTnI.

We thank the reviewer for pointing out this important aspect. We have expanded this in the discussion section as suggested (Discussion, p. 21, lines 21 – 25).

"Discussion
(…) The effect of age and sex on cut-off specificity is not only clear for hsTnT: Welsh and colleagues[11] compared cardiac troponin T and I in a large general population cohort. Despite the fact, that cardiac troponin T and I are only weakly correlated with each other and show different extent of association with cardiovascular risk factors, the 99th percentiles differ between men and women beyond the age of 70 years for both biomarkers."

4. As the author point out the increasing levels of cTnT by age have several causes. One is the increase by age itself (as illustrated that also "super healthy" elderly have higher levels) and another is the increase of comorbidities associated with chronic myocardial injury by age. Please expand a little on this in the clinical implication section.

We thank the reviewer for motivating a discussion of age-associated chronic myocardial injury and comorbidities leading to higher troponin values. Prevalence of chronic myocardial injury increases by older age. However, it is difficult to pinpoint subtle injury. In most studies, systematic screening for subclinical phenotypes is missing. We amended our discussion section by this relevant aspect (Discussion, p. 22, lines 10 to 18):

"Discussion
(…) Several causes may contribute to the age-dependent increase of hsTnT: first, age per se is important. Concurrently, our data shows consistently higher hsTnT-levels in the old and very old subjects, even if they are free of known cardiac disease and cardiac remodelling in echocardiography. However, myocardial remodelling underlies early complex processes, before macroscopic morphology and function change[12–14]. Further, comorbidities associated with chronic myocardial injury increase by age and contribute to elevated hsTnT-values[15,16]. Not all such comorbidities might have been excluded even in the "super healthy" subgroup, particularly if they are more on subclinical levels."

5. Please in the limitation section, mention the limited (understandably) number of very elderly in the cohort (see comment 1) and how this affects the interpretation.

The reviewer is right in pointing out the limitation of lower proportion of very elderly in our study. We added the following sentence in the limitation section (Limitations, p. 26, lines 27 to 29):

"Discussion
Limitations
(…)
Only 26 participants were 90 years of age or older. Therefore, estimates in the very old, particularly when further restricting to healthy subgroups, are subject to uncertainty by sparse numbers. Still, this pertains also to other studies."

Reviewer 2:

We thank the reviewer for the time and effort to review our manuscript and for the valuable remarks. We have revised the manuscript accordingly and itemize our response to each comment below.

This is a nice study of adults over 70, one with some clinical relevance and that was rigorously conducted inclusive of imaging for subclinical heart disease etc. Of course, one size should not fit all when it comes to any diagnostic biomarker; and high sensitivity troponin is no different in this regard. So, the motive for the study is sound.

We thank the reviewer for the favorable feed-back on study conduct and motivation.

However, guidelines tend to want to reduce their recommendations to as basic and memorable a form as possible (thus the attraction to often provide generic cutpoints for clinical tests), even though it is well known that things like gender and age and other comorbidities often affect the distribution of clinical test results. In the case of troponin, there is a further motivation to provide a one size fits all cutpoint, because in so doing one generally doesn't suffer in terms of sensitivity (indeed in the case of hs-troponin-T, which increases with age, the 14ng/L cutpoint is derived from a young group and so the sensitivity of this cutpoint is not harmed by applying it to older age groups). That's not to say there is no argument for making different (more personalized) cutpoints based on things like age and gender. Indeed, but applying the 14 ng/L threshold universally, the current authors show that we lose specificity in older persons. However, I would stress that for troponin, it is sensitivity that matters most. Unfortunately, the authors do not report sensitivities, because they cannot.

We thank the reviewer for describing the difficulties in balancing sensitivity and specificity of cut-off values for hsTnT in the diagnosis of non-ST-segment elevation myocardial infarction. His thoughts about this important issue stimulated a lot of further discussion among the authors. We share the reviewer's opinion, that high sensitivity is crucial for a biomarker diagnosing an acute, life-threatening disease. Specificity may be less relevant, but it is still important: low specificity implies senseless examinations, triggering further overdiagnosis, pointless hospitalization and relevant risks of serious complications during unnecessary invasive diagnostics (e.g., cardiac catheterization) [9]. Older and multimorbid patients carry a particularly elevated risk for complications from percutaneous coronary intervention [17].
We also agree that our study is not designed to provide estimates of sensitivity. For this, clinical patient data is warranted. Our study is designed to provide insights into the relatively healthy general population at old age. To give an example, our study shows, that up to two thirds of male

octogenarians show elevated hsTnT-levels above 14ng/l, albeit they do not suffer from myocardial infarction.
We thank the reviewer for the opportunity to be clearer on our study purpose and sharpened the concerned sections of our manuscript accordingly (Introduction, p. 4, lines 15 et seq.; discussion, p. 21 lines 30 et seq.):

Introduction
"(…) While high sensitivity is crucial for a biomarker diagnosing an acute, life-threatening disease with immediate options for effective intervention, specificity can also be important: low specificity implies a large proportion of unnecessary examinations, hospitalization, and cardiac catherization along with risks of serious complications[9]. Older and multimorbid patients carry a particularly elevated risk for complications from percutaneous coronary intervention[17], which emphasizes the relevance of specificity particularly for the old aged. To this extent, large population-based studies have challenged uniform cut-off values due to considerable sex- and age-differences in hsTnT-distribution with decreasing specificity by age [1,11,18]. (…)
The aims of our analyses were to understand the distribution for hsTnT-values in the mobile population ≥70 years of age without acute cardiac disease and to quantify the specificity of the 14ng/l cut-off value at old age …"

"Discussion
Clinical implications
"(…) In chest pain patients, elevated age and comorbidities are highly prevalent, as depicted by the German chest pain unit registry[4]. Both are associated with increased risk of coronary artery disease and entail a raising incidence of non-ST-segment elevation myocardial infarction[9,19]. High sensitivity is evidently crucial for a biomarker diagnosing an acute, life-threatening disease:. As missed acute cardiac ischemia is associated with considerable mortality [20], the sensitivity for hsTnT-rule out cut-off is intended to be high."

Another downside to this paper is that the hsTnT information on age is not new. See reports like https://www.jacc.org/doi/full/10.1016/j.jacc.2013.12.032 that have already demonstrated this (though the authors include more extreme ages, which is of some incremental value). My personal feeling is that this paper would be a better fit at a clinical chemistry journal.

The reviewer states, that on the one hand the association between hsTnT-values and age has already been reported, but at the other hand our study extends this knowledge to more extreme ages. While we agree that the general theme is not novel, our data provides deeper insights into the old aged (70-79 years) as well as the very old aged (80 to 95 years) individuals, which is a hitherto unreported setting. Due to the ageing of populations in industrialized countries, this old age group will increase generally and in emergency rooms. Furthermore, the coverage of this old and very old age group is limited in most other studies and clinical decision making on old aged based on data from younger individuals is potentially flawed.
Indeed, we decided for BMJ Open, as we are convinced that our data is of clinical relevance and important also for future meta-analysis of hsTnT-specificity in the elderly. We share the believe with BMJ Open, that confirmatory data is of high relevance for science and information drawn from younger samples cannot be extended to all age groups without scientific evaluation. Together, we think our study fits very well the Editorial scope of BMJ Open as outlined on the BMJ Open webpage: "Editorial decisions will not judge articles for importance, relevance or originality. Therefore, the journal will consider studies that may be judged unoriginal by other journals because they replicate in different settings work that has already been done elsewhere. It can be important to clinical practice or health policy to replicate evidence that has already been established in one type of setting".

The authors do not report on response rates among those invited to participate in AugUR, specifically in terms of how many of those invited actually attended the study. This has implications for generalizability and should be reported.

It is certainly important to report on response ratio. We provide now further details in the methods section (methods, p.6, lines 4 et seq.):

“Methods
Study sample

The design of the German AugUR study (Age-related diseases: understanding genetic and non-genetic influences – a study at the University of Regensburg) has been described in detail previously[21]. Briefly, we recruited inhabitants at least 70 years of age in the city of Regensburg, Germany, and selected nearby counties. via a random sample from tThe local registries of residence provided a random sample of 5,971 subjects’ postal addresses, who Participants were invited by mail. Of these, (i) 327 persons were not contactable, as they had moved outside the study region or had meanwhile died, (ii) 3,187 persons did not respond, (iii) 1,324 responded negatively (i.e., declined participation by phone or in writing), and (iv) 1,133 participated (response among the 5,644 contactable =20.1%). For 402 non-participants, the specified reasons for denial were: 56.5% too ill, 6.2% no time, 20.1% no interest, 17.2% other.”

We totally agree with the reviewer’s remark, that response rate implies implications for the generalisability of our study. The results are not generalizable to the full population aged above 70. Our participants reflect a mobile proportion of the old aged as outlined in the methods (see above). We expanded the discussion on this (limitations, p. 25 lines 3 et seq.):

“Discussion
Limitations:
The response proportion of the AugUR-study was 20.1% percent. It is similar to other recently established studies, even when they focused on more moderately aged adults[22]. By our design and recruitment strategy, there is a selection towards healthier subjects: our participants had to be mentally and physically fit enough to travel to the study center and to answer all interview questions personally. This is mirrored by the fact, that 56.5% of non-participating subjects, who specified their reason for non-participation, declared, that they felt too ill to participate. Therefore, our participants do not represent the full old aged population, but reflect the “mobile” population aged above 70years. For the aims of these analyses, this selection is advantageous, as we were interested in the relatively healthy old aged. Our data from medical exams including cardiac ultrasound, detailed medication intake history, and biomarker assessment enabled a further restriction to “healthy” old aged sub-cohorts.”

In terms of the health subgroup analyses, I agree with the author’s exclusions; however, I think they should consider also excluding persons with significantly elevated BP at the study exam (say BPs >140/90 and certainly >160/100 mmHg) from subcohorts 2 and 3. See these papers. https://pubmed.ncbi.nlm.nih.gov/25880403/ https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.114.014364. The authors don’t need to exclude persons with HTN or on BP meds, to do so would be implausible for such an old sample, however, excluding very elevated blood pressures at the time of biomarker testing is probably warranted for the health subgroup analyses.

We thank the reviewer for this relevant aspect. Indeed, the association of hsTnT-levels and acutely elevated blood pressure is known and relevant for our analyses and interpretations. We re-did our analyses additionally excluding subjects with significantly elevated blood pressure at the study exam

(>160/100mmHg) and revised the corresponding paragraphs and Table 5 accordingly (Results, p. 17, lines 6 et seq.; Table 5 p. 15 et seq.; Discussion p.21 lines 10 et seq.):

“Results:
Specificity of the rule-out upper reference limit (14ng/l) in healthy subgroups
Next, we evaluated the specificity of 14ng/l hsTnT cut-off value in a healthy subgroup of our study participants (Table 5): in subjects free of clinical coronary artery disease, heart failure or impaired renal function (subcohort I, n=618) specificity increased to 79% compared to the 68% in all participants. This proportion barely changed by additional exclusion of diabetic and obese participants as well as subjects with a measured blood pressure >160/100mmHg (83%; subcohort II, n=408 366). To further account for subtle, asymptomatic cardiac disorders, echocardiographic data was used to finally analyse a subgroup additionally free of any of the following: (i) no left ventricular hypertrophy (left ventricular mass to body surface area >115g/m^2 for men; 95g/m^2 for women)[23], (ii) no elevated left ventricular filling pressure (E/mean e’ > 14)[24] and (iii) no left ventricular systolic dysfunction (ejection fraction < 50%)[25]. In the resulting subgroup (subgroup III, n=10 96), specificity increased to 901%, whilst remaining poor in participants above 79 years of age (50 5%).
Together, the specificity of the endorsed rule-out cut-off hsTnT-value for acute non-ST-segment elevation myocardial infarction ranged between 79% to 90 1% in the healthy subgroups.”

“Discussion
Indeed, these values have to be interpreted with caution, as several illnesses with increasing age-dependent prevalence are per se associated with elevated hsTnT-levels, e.g. impaired kidney function, obesity, diabetes mellitus type II and irregular heart rhythm [11,26,27]. Furthermore, elevated hsTnT-levels are linked to elevated blood pressure[28,29] as well as signs of subtle, non-overt cardiac disease with increasing prevalence in the elderly, as increased left ventricular filling pressure [30] and left ventricular hypertrophy[31]. However, even in our reasonably healthy sub-cohort free of pre-existing cardiac disease, i.e., free of all discussed comorbidities and having blood pressure below 160/100mmHg, associated with higher hsTnT-levels as well as of echocardiographic signs of non-overt heart disease, the 99th percentile is calculated as 2931ng/l and thus more than twice as high as the recommended rule-out cut-off value of 14ng/l,. In the very healthy sub-cohort, that is additionally free of echocardiographic signs of non-overt heart disease, specificity of the 14ng/l cut-off value is down to 90% which just represents the 91st percentile even in the very healthy elderly.”

	n	99th hsTnT percentile [95% CI]	95th hsTnT percentile [95% CI]	Proportion below hsTnT 14ng/l
All	1,129	54 [44 - 74]	29 [26 – 31]	68
Stratified by sex				
Women	509	38 [27 - 79]	22 [20 - 23]	82
Men	620	64 [46 - 102]*†	31 [29 - 36]*‖	57
Stratified by sex and age				
Women 70-79 yrs	375	29 [23 - 58]	19 [15 - 21]	88
Women 80-95 yrs	134	67 [39 - 79]	27 [22 - 39]	66
Men 70-79 yrs	433	70 [42 - 281]*‡	30 [26 - 33]*¶	67
Men 80-95 yrs	187	59 [52 - 75]	37 [31 - 46]	34
Stratified by kidney function				
eGFR ≥ 60	778	33 [30 - 36]	24 [22 - 26]	76
eGFR < 60	338	77 [56 - 308]*§	44 [34 - 53]*Δ	50

Subcohort I				
All	618	32 [28 - 33]	22 [21 - 25]	79
Stratified by sex				
Women	289	25 [21 - 41]	17 [15 - 20]	90
Men	329	32 [30 - 33]	25 [23 - 28]	70
Stratified by age group				
70-79 yrs	507	30 [26 - 33]	21 [19 - 23]	83
80-95 yrs	111	40 [31 - 41]	28 [23 - 32]	62
Subcohort II				
All	366	31 [26 - 33]	20 [17 - 23]	83
Stratified by sex				
Women	173	22 [21 - 22]	16 [14 - 20]	90
Men	193	33 [31 - 33]	25 [18 - 29]	77
Stratified by age group				
70-79 yrs	304	30 [22 - 33]	18 [15 - 21]	88
80-95 yrs	62	N/A	29 [22 - 33]	60
Subcohort III				
All	96	N/A	17 [14 - 25]	90
Stratified by sex				
Women	49	N/A	17 [11 - 20]	94
Men	47	N/A	23 [14 - 29]	85
Stratified by age group				
70-79 yrs	86	N/A	14 [12 - 20]	94
80-95 yrs	10	N/A	N/A	50

Table 5: The 99th and 95th percentiles of high-sensitivity troponin T and percentiles corresponding to the recommended rule-out cut-off for non-ST-segment elevation myocardial infarction (14ng/l). Shown are 99th and 95th percentiles with 95% confidence intervals in the entire AugUR study sample (all) with further stratification for sex, age and renal function, as well as in subcohorts free of overt heart disease and impaired renal function (subcohort 1), comorbidities associated with elevated hsTroponinT (diabetes, obesity; subcohort 2) and subtle cardiovascular disease measurable by echocardiography (subcohort 3).
Subcohort I: subjects free of clinical coronary artery disease and heart failure with normal renal function (eGFR≥60ml/min/1.73m^2).
Subcohort II: as subcohort I, additionally free of diabetes and obesity (body-mass index <30 kg/m^2) with a blood pressure <160/100mmHg at study visit.
Subcohort III: as subcohort II, additionally in regular heart rhythm, free of left ventricular hypertrophy, of elevated left ventricular filling pressure (E/e' > 14) and of left ventricular systolic dysfunction (EF < 50%).
*Leave-one-out analyses revealed an influential observation: one man (age 77years, eGFR 59ml/min/1.73, no coronary artery disease, LVMi 117g/m2, EF 65%) exhibited an extraordinarily elevated hsTnT-level of 421ng/l. Excluding it, percentiles and 95% confidence intervals were lowered to †57 [46 - 75], ‡63 [38 - 101] and §74 [55 - 93] for the 99th percentiles in ng/l [95%CI] and $^{\|}$ 31 [30 - 33], ¶ 29 [26 – 33] and $^{\Delta}$43 [33 – 49] for the 95th percentiles in ng/l [95%CI].
Left ventricular hypertrophy: left ventricular mass to body surface area >115g/m2 for men / 95g/m2 for women. E/e': ratio of the transmitral early peak velocity by pulsed wave Doppler over mean early diastolic velocity determined at the septal and lateral mitral annulus by tissue Doppler. EF: ejection fraction. $eGFR_{crea}$ glomerular filtration rate estimated from serum creatinine [ml/min/1.73m^2].

Although they can by intuited from the legend/title, the statistical methods used in figure 3 are not described in the statistics section and should be.

We thank the reviewer for pointing us towards a gap in our methods section: we added the corresponding paragraph to the methods section (methods, p. 9 et seq.):

“Odds ratio estimates for hsTnT-values > versus <= 14ng/l were computed by simple logistic regression for each of the covariates separately: age, male sex, impaired kidney function, type II diabetes, history of coronary artery disease, left ventricular hypertrophy, diastolic dysfunction, left atrial hypertrophy and elevated filling pressure (defined as E/e’>14). This was repeated adjusting for age and sex, as applicable. “

Minor comment. Page 2, line 5, would ‘ambulatory’ be better than ‘mobile’? Also, same goes for page 2 lines 9 and 13, indeed throughout the entire paper.

While we agree with the reviewer that the term “mobile” is not standard terminology and not fully clearly defined, we think that “ambulatory” is usually connotated with “patients”. To avoid any allusion to a study in “patients”, we would like to stick to the “mobile”. To clarify the meaning, we have introduced this terminology and its meaning here:

“Methods

The 1,133 participants were able to come to the study centre at the University Medical Centre, to walk around independently, to answer all interview questions personally, and to conduct a two-hour study program including non-invasive medical exams. Thus, all participants had no acute cardiac events, were physically mobile and mentally fit. We consider our participants to reflect the “mobile” old aged population.”

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VERSION 2 – REVIEW

REVIEWER	Lindahl, Bertil Uppsala Clinical Research Center
REVIEW RETURNED	05-Sep-2021

GENERAL COMMENTS	The authors have responded adequately to mine and the other reviewer´s comments. I have only one minor comment: Please state the 25th and 75th percentile level in stead of the IQR. the 25th and 75 th percentile level contain more valuable information to the reader.

REVIEWER	McEvoy, John John Hopkins University School of Medicine, Medicine, Cardiology
REVIEW RETURNED	27-Aug-2021

GENERAL COMMENTS	The authors do a good job in their response letter and in revising the paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

The authors have responded adequately to mine and the other reviewer´s comments.
I have only one minor comment: Please state the 25th and 75th percentile level instead of the IQR. The 25th and 75th percentile level contain more valuable information to the reader.

We thank the reviewer for the time and effort to review our revised manuscript and for the valuable remark. We endorse the reviewer's view and replaced accordingly the interquartile range by reporting the 25th and the 75th percentile.

Reviewer 2:

The authors do a good job in their response letter and in revising the paper.

We thank the reviewer for the time and effort to review our revised manuscript and for appreciating our revision.